received 99 courses of ZD9331 over 8 dose levels: 2.5, 5, 10, 20, 30 and 40 mg once daily for 5 days, 10 mg twice daily for 5 days and 10 mg once daily for 10 days, respectively, repeated every 3 weeks. One pt treated at 40 mg/day, 2 pts treated at 20 mg/day (bid), and 1 pt at 10 mg for 10 days developed grade 3–4 neutropenia and/or thrombocytopenia. Non-haematological toxicity was usually mild and included nausea/vomiting, stomatitis, diarrhea, myalgia/arthralgia, fever, and alopecia. Transient asymptomatic rises in liver transaminases occurred at all dose levels. Skin rash occurred in 23% of cycles. Pharmacokinetics (PK) demonstrated a saturable absorption of ZD 9331 from doses of 20 mg once daily onward, precluding further dose escalation. Twice daily dosing did not significantly increase exposure compared with a once-daily administration. PK analysis at the 10 mg × 10 days schedule is still on going. Preliminary plasma deoxyuridine data indicate that they can be used as a marker for TS-inhibition.

1168 POSTER

Phase I trial with farnesyltransferase inhibitor R115777 in patients (pts) with advanced solid tumors

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Purpose: The critical modification needed for the ras protein to exert its function is farnesylation, which can be blocked by R115777, a potent and selective orally bioavailable non-peptidomimetic inhibitor of farnesyltransferase. This study was designed to determine the MTD of a 28-day bid oral regimen.

Methods: R115777 is given according to an intra- and inter-pt dose-escalation scheme with 1–6 pts per dose level depending on toxicity. Each 28-day cycle (C) is followed by a 7–14 d restperiod. Starting dose was 200 mg bid, increased with 100 mg bid with a maximum of 2 intra-pt dose escalations. DLT was defined as grade 3–4 toxicity or treatment delay >3 wks.

Results: Sofar 7 pts have been treated, median age 58 yrs, all had received previous chemotherapy. One pt had grade 4 leucopenia at 300 mg bid in C1, and this cohort was expanded to 6 pts. One pt in this cohort had grade 4 leucopenia at 500 mg bid. At 300 mg bid one pt had grade 3 diarrhea in C2 and one pt grade 3 fatigue in C1, possibly related to R115777. One pt with gastric cancer has an ongoing SD for 8 months. PK of R115777 was assessed in C1 for the 1st 12 h dosing interval on day 1 and 28 and was measured by a validated HPLC method. Peak concentrations ranged from 431–800 ng/ml and were obtained within 2–5 h. Trough levels ranged from 29.3–98.7 ng/ml. There was little accumulation, and steady-state concentrations were maintained throughout the dosing period.

Conclusion: Recruitment continues to determine MTD and to confirm whether leucopenia is dose-limiting.

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Phase I trial of a three-day schedule of cisplatin plus topotecan

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Purpose: Topotecan (tpt) is emerging as a new chemotherapy option in the treatment of lung and ovarian cancer. Preclinical data suggest a sequence dependent synergy of tpt with cisplatin but a clinically acceptable sequence-schedule of these two agents has yet to be defined. We conducted a phase I study of a convenient and logistically feasible daily ×3 schedule. By splitting the dose of cisplatin over three days we aimed to a more favourable toxicity profile and a possibly better pharmacological inter-reaction of the two agents. Main objectives were to define the maximum-tolerated dose (MTD) and dose limiting toxicity (DLT) and to characterise the toxicity profile of this regimen.

Methods: The standard for phase I entry criteria and definitions for MTD and DLT were applied. Both agents were administered intravenously on a daily ×3 basis every 3 or 4 weeks with or without G-CSF. Cisplatin was given first with hydration followed by topotecan two hours later. At present 18 patients (4 F/14 M, median age 58, range 30–72) have been treated and a total of 49 courses have been given at four dose-levels: cisplatin/tpt: 25/0.75 – 25/0.9 -25/1- 25/1.15 mg/m^2/day.

Results: Myelossupression was the DLT as expected. With cisplatin at 25 mg.m−2 daily dose the MTD of the combination was 25/1.15 at which 2/2 patients developed febrile neutropenia and grade 4 thrombocytopenia each one respectively. Febrile neutropenia also occurred in 1/6 patients at dose levels 25/0.9 and 25/1. Both were carboplatin-pretreated pts and succeeded to continue treatment with G-CSF support. At these levels a short-lived grade 2 or 3 neutropenia was seen in half of the patients and grade 3 thrombocytopenia was infrequently observed but tended to be cumulative in pretreated patients. Non-haematological toxicity was unremarkable. Efficacy was documented in 3 lung and 1 ovarian case.

Conclusion: A three-day schedule of the cisplatin plus topotecan combination is well tolerated with mainly haematological toxicity. With cisplatin at 25 mg.m−2 daily dose the MTD of the combination is 25/1.15 and the optimal 25/1. The study is in progress investigating the combination at 20 mg.m−2 fixed daily dose of cisplatin.

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Phase I pharmacokinetic study of MEN-10755 in solid tumors

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Purpose: In a phase I and pharmacokinetic study the safety profile of MEN-10755 (MEN) was evaluated. MEN is a novel anthracycline showing in the animal models an improved therapeutic efficacy over doxorubicin, especially in breast, ovarian and lung cancer.

Patients & methods: Eligible patients (pts) had incurable cancer, performance status ECOG ≤ 2, no prior anthracyclines and LVEF ≥50%. MEN was administered as 15 min iv infusion once weekly for 3 weeks, followed by 1 week rest. Starting dose was 15 mg/m^2 per infusion and was escalated to 30 mg/m^2 and up to 45 mg/m^2 per infusion. Plasma and urinary MEN levels were measured by HPLC with fluorescent detection.

Results: Until now, 8 pts were entered. Anemia grade (gr) 1–3 occurred in 7 pts, anemia gr 4 in 1 pt at 30 mg/m^2, thrombocytopenia gr 1 in 1 pt at 30 mg/m^2. Two pts had leukopenia gr 1 at 30 mg/m^2. At 45 mg/m^2, in 2 pts the third infusion day 15 was omitted because of ANC ≤1000/mm^3. These pts also had leukopenia gr 3. Nausea/vomiting gr 1–2 occurred in 4 pts, gr 3 in 1 pt at 45 mg/m^2. During infusion 2 pts had flushing gr 2. Most pts experienced alopecia gr 1. No significant LVEF reduction has been observed. AUC was correlated with dose. Mean $AUC_{0\rightarrow\infty}$ for 30 mg/m^2 = 6.0 mg/L.h. Mean values (all doses) were: $t_{\frac{1}{2}\beta}$ = 15.2 ± 3.6 h, CL = 5.6 ± 0.9 L/h/m^2, Vss = 81.2 ± 23.5 L/m^2. Mean renal clearance was 4.4 ± 2.1%.

Conclusion: Neutropenia day 15 was dose limiting at 45 mg/m^2/infusion. Currently 40 mg/m^2/infusion is evaluated.

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Pharmacology study of chronic oral idarubicin for breast cancer

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Purpose: To investigate new modalities of IDA administration, we designed a phase I study of IDA given orally in hyperfractionated doses. The purpose was to determine the maximum-tolerated dose (MTD), toxicity profile, and pharmacokinetics of IDA with this schedule.

Methods: Patients with metastatic breast cancer relapsed after standard therapy (including anthracyclines). The initial dose of IDA was 2 mg/d given orally in two doses every 12 hrs for 21 days every 28 days. Subsequent dose escalations were in increments of 1 mg/day. Dose limiting toxicity (DLT) was defined as G4 hematologic toxicity or any other toxicity ≥G3. Pharmacokinetic parameters were calculated using a noncompartmental model.

Results: Thirty-one patients were enrolled. IDA was escalated from 2 mg/d to 10 mg/d and MTD was reached at this dose level; DLTs were neutropenia (G4) associated with leukopenia and piastrinopenia in 1 patient and diarrhea (G3, 1 patient) out of 5 patients. Both IDOL and IDA exhibited linear pharmacokinetics over the dose range studied. The median $AUC_{(0-24)}$ of IDA increased from 3.95 μg*h/L (range, <2.4 to 6.9 μg*h/L) to 15.2 μg*h/L (range, 14.2 to 18.4 μg*h/L) when the dose was increased from 2 to 10 mg/d. The median $t_{1/2}$ for IDA was 21.2 hours (range, 11.3 to 49.7 hours), whereas $t_{1/2}$ for IDOL was much longer (median, 50.0 hours; range, 22.7 to 85.3 hours). IDA/IDOL ratio in plasma (median, 8.3; range, 5.4 to 16.5) was not dose-dependent.